

ACUTE MYELOID LEUKEMIA IN ELDERLY PATIENTS

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Acute myeloid leukemia (AML) is a disease affecting especially elderly patients. The incidence of the disease increases with age. According to epidemiological data the incidence increases from 1/100000 in young adults (<40 years) up to 15/100000 in patients over 75 years old^{1,2,3}. Thirty-five percent of newly diagnosed patients are aged > 75 years and the median age at diagnosis is 67-69 years^{4,5}.

The outcome of elderly patients is much poorer than that of younger patients, as shown by multiple studies that demonstrated that age 60 years is an independent negative prognosis factor in multivariate analysis^{5,6}. This is also shown by the shorter long term survival (only 3-8% at 5 years) of elderly patients compared to almost 50% in younger patients^{5,7}.

AML in older adults seems to have clinically and biologically distinct characters translated by worse treatment outcome compared to patients younger than 60 years. This pattern of evolution is due to some patient specific factors as well as age-related factors^{2,4,7}.

Compared to younger patients, AML in elderly arise frequently after myelodysplasia or secondary to chemo-/radiotherapy for another malignancy. This could be related with the observation that AML in elderly is a less proliferative disease expressed through lower counts of white blood cells and blasts in blood and marrow^{2,4,7}.

Leukemic cells in elderly are characterized by features that are different from those of young patients:

- a more frequent expression of stem cell related antigens (CD34)⁸,

- a high percentage of poor prognosis cytogenetics. In the elderly the incidence of unfavourable cytogenetic abnormalities (-7/7q-, -5/5q-, 17p anomalies, complex karyotype) is over 30% and can reach up to 50% in patients > 75 years compared to young patients where it accounts for only 10-15%^{5,7,9}. Conversely, cytogenetic alterations associated with good prognosis (t(15;17); t(8;21); inv(16)/t(16;16)) account for at most 5% of elderly AML cases, while they are present in 25-30% of younger AML patients^{5,7,8,9}.

- gene expression profile. During the last years, a number of acquired gene alterations associated with prognostic significance have been identified. Like in younger patients, cytogenetically normal AML elderly patients with a NPM1 mutation or a bi-allelic CEBPA mutation lacking FLT3 mutation have relatively

favourable prognosis^{7,10}. Some other recurrent genetic alterations like TET2 and IDH2 seem to be more common in older patients⁵. Recent studies revealed that AML presenting at older age showed distinct gene expression profiles such as the downregulation of the tumor-suppressor p16INK4A and a higher probability of RAS, Src and TNF pathway activation associated with decreased sensitivity to anthracyclines^{5,7,11,12}.

- resistance to standard chemotherapy explained by a more common expression of MDR1 glycoprotein^{3,5}.

Other factors are age-related such as comorbidities, impaired bone marrow stem cell reserve, with poor tolerance to myelosuppressive chemotherapy.

All these factors could explain why the current chemotherapy-based treatment of older adults with AML has disappointing results: CR rate is <45% (compared to 75% for younger patients), treatment related mortality is ~ 25%, median overall survival is ~ 10 months, the relapse rate is high and only 10% of cases have long survival³.

These disappointing results are a major challenge in the therapy of these patients and call for more effective and less toxic treatment strategies.

Recent results of clinical studies showed that intensive treatment even in elderly patients is superior in terms of response rate and survival than low-dose treatment or best supportive care^{13,14}.

Currently, the most used and associated with best results chemotherapy is the "7+3" combination¹³. Clinical trials are evaluating other therapy approaches in order to improve induction results:

- higher daunorubicin doses 15 or use of other anthracyclines in standard or higher doses¹⁶; this study showed a higher CR rate for higher anthracycline doses but without impact on overall survival; the most important conclusion of this study was that elderly patients can tolerate anthracyclines and that there is no ground to decrease doses in patients with good clinical condition^{5,13};

- association of MDR inhibitors (Cyclosporine or analogs) – without significant results⁵;

- monotherapy/combinations containing clofarabine – ongoing studies^{5,17,18}.

After obtaining CR, there isn't a consensus regarding postremission therapy for elderly patients, though several approaches are under investigation:

- consolidation chemotherapy – controversial

results. Recent studies showed no superiority of intensive consolidation (1 vs 4 cycles) compared to less intensive but longer therapy (e.g. monthly courses of lower doses Ara-C and anthracyclines) 20.

- Reduced intensity conditioning hematopoietic stem cell transplantation (RIC-HCT) is a promising alternative for patients over 70 years with good clinical condition. There are still debates regarding the improvement of RIC-HCT outcome by reducing the toxicity of conditioning (using clofarabine or radiolabeled antiCD45 antibodies) or by improving antitumor immunologic activity (specific T cells directed against LAM – WT1 specific antigens or against minor histocompatibility complexes on receptor hematopoietic cells) 21.

- Immunologic approach – IL-2 associated with histamine 21.

A major problem is that of older patients who cannot tolerate intensive therapy because of comorbidities, clinical condition, age. Clinical studies showed that for this patients treatment, even with low doses, is superior in terms of response rate and survival than supportive care 13,14.

In these cases, low-dose approaches are used such as low dose cytarabine, or other therapies that are under investigation: low-dose mercaptopurine valproic acid, gentuzumab ozogamicin or clofarabine + low dose cytarabine, hypomethylating agents (azacitidine, decitabine), laromustine 5,13,17,18.

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